

Neuronal energy consumption: biophysics, efficiency and evolution

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Electrical and chemical signaling within and between neurons consumes energy. Recent studies have sought to refine our understanding of the processes that consume energy and their relationship to information processing by coupling experiments with computational models and energy budgets. These studies have produced insights into both how neurons and neural circuits function, and why they evolved to function in the way they do.

Addresses

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Introduction

Neurons consume energy. Appreciating that they do so is essential for understanding and interpreting the function and evolution of neurons, neural circuits and, ultimately, whole brains. Yet we must go beyond mere appreciation by relating specific molecular components and processes to the energy they consume and the work they contribute to processing information and generating behavior. This permits determination of both ‘how’ and ‘why’ processes consume energy, and an understanding of the key trade-offs that have influenced neural evolution (reviewed in [1,2]). Although neuronal energy consumption has been studied for over 80 years [3,4], conceptual and methodological breakthroughs [5-9] have prompted renewed interest in the causes and consequences of neuronal energy consumption over the last ~20 years. Here I review this recent progress in our understanding of how the physiology and anatomy of neurons and neural circuits reflect fundamental relationships between energy consumption, biophysics and performance.

Major energy consuming processes in neural tissue

The nervous system is a major energy consumer; the human brain, for example, consumes 20% of basal metabolic rate, whilst accounting for just 2% of the body mass [10]. Experimental, theoretical and computational approaches (Box 1) have shown that the primary processes within adult neurons and neural networks that consume energy are the generation and maintenance of electrical signaling and synaptic transmission [7-9,11-15]: The vast numbers of ions moving across the cell membrane to produce electrical signals, whether post-synaptic/graded potentials or action potentials, must be restored by the $3\text{Na}^+/2\text{K}^+$ pump [16]. For every three Na^+ ions extruded an ATP molecule is hydrolyzed to provide energy for the work of the pump. Other processes, such as neurotransmitter re-uptake or Ca^{2+} extrusion, are often linked to the work of the pump through symporters and antiporters that co-transport Na^+ or K^+ ions. One exception to this is the loading of synaptic vesicles, which involves a V-ATPase [17].

Resting, 'housekeeping' and developmental costs

Costs are incurred even when a neuron is 'at rest' just to maintain the resting potential because ions are moving across the membrane, albeit at a lower rate than when signaling [8,12]. These resting costs are typically substantially lower than the signaling costs, though there are exceptions such as vertebrate photoreceptors [15]. The precise relationship between resting and signaling costs can influence the way in which information coded within populations of neurons, relatively low resting costs favoring large populations that are rarely active producing sparse coding (see below) [1,7,18].

Even in adult neurons processes linked to 'housekeeping' or cellular maintenance also consume energy [19,20]. The specific processes and their contributions have yet to be identified fully, and those that have been investigated have revealed some surprises. For example, protein synthesis appears to consume relatively little energy, whilst lipid synthesis consumes a higher proportion of the cellular housekeeping costs [20]. Another factor likely to be contributing a substantial amount to non-signaling energy consumption is mitochondrial proton leak, which erodes the proton motive force established by the respiratory electron transport chain [1,20,21].

In developing neural tissue, the division of costs is likely to be rather different because the production of new tissue will consume substantial amounts of energy, though these costs may still be small in comparison to long-term operation of neural tissue. For example, incorporating developmental energy consumption into an energy budget of cortical white matter suggests that the cost of building myelin could be repaid rapidly through savings in action potential energy consumption were it not for the energy cost of maintaining the oligodendrocyte resting potential [22]. This suggests that the role of myelin is in increasing propagation speed rather than in reducing energy consumption.

Linking energy consumption to performance

Energy consumption within neurons and neural networks is linked to their performance through signaling speed, noise, and propagation (reviewed in [1,2]). The signaling speed (or bandwidth) of a neuron depends upon its membrane time constant. Reducing the time constant increases the bandwidth but requires an increase in conductance, which increases the ionic current that flows. This inflates energy consumption because more ions are move across the membrane creating more work for the $3\text{Na}^+/2\text{K}^+$ pump.

Noise, random fluctuations or distortions that interfere with a signal, may arise from stimuli extrinsic to a neuron (e.g. sensory stimuli or neurotransmitter molecules), or from intrinsic processes (e.g. spontaneous activation of voltage-gated ion channels) (reviewed in [23]). Signals can be protected from noise through amplification but this involves greater numbers of molecules and, consequently consumes more energy. Noise can also be removed by averaging across signaling events, provided that the noise is independent in each of the events being averaged. Averaging to remove noise can be implemented on different scales from increasing the number of ion channels generating a signal within a neuron or the number of vesicles released at a synapse, to the number of neurons within a circuit signaling in parallel. Irrespective of the scale, however, greater numbers of events consume more energy.

Once generated, signals must be propagated to permit information processing and transmission. Irrespective of whether these signals are graded potentials or action potentials, propagation consumes energy because ions flow across the cell membrane. The precise amount of energy consumed depends upon the distance over which signals are propagated as well as the biophysical properties of the neuron, emphasizing that the effects of bandwidth, noise and propagation on neural energy consumption cannot be fully disentangled from one another.

Action potential energy consumption

Most, though not all [24], neurons use action potentials to transmit information over long distances. This is not, however, their sole function; action potentials are also important for preventing noise accumulation in successive layers of information processing in neural circuits. The energy consumption of a single action potential within a single neuron would be challenging to measure directly, so typically it is estimated by converting the electrical signals into the total amount of work the $3\text{Na}^+/2\text{K}^+$ pump must do to restore ion gradients (Box 1) [9,25-36]. Estimates of action potential energy consumption are, consequently, dependent upon accurate measurement of biophysical parameters including channel kinetics, conductance magnitudes and membrane capacitances.

Heterogeneity in action potential costs

Initial estimates of action potential energy consumption were based upon that of the squid giant axon [9,25]. It was assumed that the energy consumption of this action was broadly representative of other action potentials [9]; however, this was dispelled by combining experimental measurements and computational modelling of a range of action potentials primarily from mammalian neurons [26-29]. This demonstrated that the squid giant axon action potential was profligate in its energy consumption compared to most other action potentials, and revealed a hitherto unappreciated heterogeneity in the biophysics of the currents generating action potentials and their consequences for the energy consumption of the action potential [25-36]. The major cause of differences in energy consumption was identified as the overlap between the inward and outward currents during the action potential [26,28,34,35]: A large overlap inflates energy consumption whereas complete separation of the currents reduces energy consumption close to the minimum possible. The extent of the overlap is determined by the biophysical properties (e.g. kinetics, sensitivity) of the voltage-gated ion channels that generate the action potential; faster Na^+ channel inactivation and the delayed onset of K^+ channel opening reduces overlap [28,34,35]. With sufficiently fast kinetics, Na^+ -activated K^+ channels can also contribute to the production of energy efficient action potentials [36]. Why such heterogeneity in action potential energy consumption exists remains unclear, though it may be a consequence of signaling constraints and the need for reliability.

Re-evaluation of energy budgets

Budgets that estimate the energy consumption of neural tissue from the ‘bottom-up’ are susceptible to errors because they are based on assumptions about the molecular processes that occur in single neurons (Box 1). To avoid this, most energy budgets are verified by independent experimental measurements of energy consumption [e.g. 9]. Nevertheless, many energy budgets incorporate the assumption that the energy consumption of mammalian action potentials is equivalent to that of the squid giant axon action potential [e.g. 9,37-39]. Following the discovery that mammalian action potentials consume far less energy, these energy budgets had to be revised because they overemphasized the action potential energy consumption [28,40]. The revised energy budgets instead show that synaptic transmission and postsynaptic potentials actually consume a higher proportion of the total energy consumption of the grey matter. Some energy budgets [9,37] had also estimated the average rate of spiking that could be sustained within neural tissue. Again, these rates had to be revised upwards, albeit only slightly, to reflect the lower cost of mammalian action potentials.

Energy efficiency of information coding

The coding of information in many neurons and neural circuits is consistent with having been under selection for energy efficiency, from the biophysics underlying the electrical events themselves to the strategy of representing information [1,2]. Increased efficiency can be achieved by making the signals

that encode information cheaper or by adopting coding schemes that requires fewer signals: Both strategies are present in nervous systems.

Intrinsic biophysical properties of neurons

Given that ion movements dominate signaling costs it is unsurprising that channel properties (e.g. kinetics and sensitivity), and the combination of channels expressed, are major determinants of the energy consumption of electrical signals, including action potentials (see above) [28,33-36,41]. Various other cellular properties also contribute to signaling costs including the size and shape of neurons [12,42,43], which affects their capacitance and resistance and, consequently, their bandwidth, signal-to-noise ratio (SNR) and distance over which signals must spread throughout them. Experimental measurements and computational modelling suggest that smaller neurons have lower information rates than larger homologous neurons (Box 2) [12,42]. Indeed, computational modelling also shows that for a given cell size, there is one channel density that maximizes information but that energy efficiency is maximized at lower channel densities [42]. Voltage-gated ion channels can also affect the coding scheme implemented in neurons by altering the threshold for action potential generation or whether action potentials are generated at all (see below).

Synaptic inputs

Synaptic inputs to neurons also affect the energy efficiency of information coding [44-46]. The properties of ligand-gated ion channels and receptors expressed on the post-synaptic membrane will affect both the information content of post-synaptic potentials and the energy they consume. Experiments and computational modelling have demonstrated that the exact size of synaptic inputs to a neuron affects the information rate [e.g. 42,46]. Larger synaptic inputs increase signal amplitude relative to intrinsic noise and, consequently, produce higher information rates but do so at higher costs producing a law of diminishing returns (Box 2). Consequently, whilst the highest information rates are produced by large synaptic inputs, the highest energy efficiency is achieved with smaller inputs.

Synaptic inputs also affect the neuronal conductance influencing energy consumption [47]. Increased conductance can reduce gain whilst making the membrane faster, extending bandwidth, and ensuring that action potentials occur more reliably. Balanced excitatory and inhibitory synaptic currents, which occur in many cortical neurons *in vivo* (reviewed in [48]), demonstrate the impact of synaptic conductances on energy efficiency. Computational modelling shows that single compartments receiving balanced excitatory and inhibitory synaptic currents achieve similar information rates to those receiving only excitatory inputs (or balanced excitatory and inhibitory conductances) but do so with fewer action potentials and, therefore, lower energy consumption [47]. More generally, this suggests that the precise combination of synaptic inputs can produce fewer, more informative action potentials increasing both coding efficiency and energy efficiency.

Graded *versus* pulsatile coding

Information can be represented within neurons as both graded and pulsatile (action potentials) electrical signals [8,49,50]. This difference typically arises because graded neurons and dendrites either lack voltage-gated Na⁺ or Ca²⁺ channels or do not express them at sufficient densities [8,49]. Graded potentials encode more information per unit time than pulsatile codes, and the conversion from graded to pulsatile produces information loss accompanied by a drop in energy efficiency [8,49,50]. Computational models show that information loss is due to increased intrinsic noise and non-linearity produced by the channels generating the action potential, as well as the duration of the action potentials themselves, which obscure the underlying graded signal [48]. Reduced efficiency is a consequence of information loss coupled with the cost of generating action potentials. Yet neurons must pay this two-fold cost to generate action potentials because graded signals degrade over long distances and are susceptible to accumulating noise [8,49].

Efficient coding schemes and strategies

Numerous coding schemes and strategies have been linked to improving the energy efficiency of information processing (reviewed in [1,2]). Indeed, the high costs of action potentials mean that schemes promoting coding efficiency by increasing the information content per action potential are likely to also increase energy efficiency. Thus, coding strategies that filter out information unnecessary for generating adaptive behavior [51,52], or which can be predicted [53-55], simultaneously improve both coding efficiency and the energy efficiency of information coding. These strategies are most obvious in the sensory periphery, where matched coding ensures that rather than capturing broadband information, specific information is extracted [2,51,52]. Predictive coding, in which fewer resources are invested in extracting and processing expected inputs than in novel inputs, is another means of improving energy efficiency through coding efficiency [2,53-55]. The reduced encoding of redundant information in the periphery also produces further energy savings in higher processing areas.

Other strategies are implemented in populations of neurons by making use not just of information coding in action potentials but also the presence of cells that remain silent [56]. The relatively low energy cost of resting potentials compared to action potentials favors this sparse coding of information across populations of neurons, in which information is represented within a small subset of active neurons [1,18]. However, as resting costs increase in relation to signaling costs, denser coding of information in fewer neurons is favored [1,18]. Both synaptic inputs and voltage-gated ion channels can alter the relationship between resting costs and signaling costs [28,47,49] and, consequently, the energy efficiency of sparse coding in neural populations. Noise also constrains coding efficiency potentially preventing neuronal populations from implementing the most efficient codes and, consequently, reducing the energy efficiency of information coding (reviewed in [23]). For example, in populations of neurons encoding natural stimuli low spike rates are used less often than predicted because of their low reliability, causing a deviation from the maximally efficient coding scheme in which spike rates are distributed exponentially [57,58].

Another means of increasing the energy efficiency of information coding is to differentially invest resources both spatially and temporally within neurons and neural circuits (reviewed in [2]). Unlike fixed matched filters in the periphery or implementing specific predictive coding schemes, the adaptive filtering of signals can be flexibly controlled and coupled to behavior (reviewed in [59]). Consequently, the limited energy available for information processing and transmission can be placed where needed for the generation of adaptive behavior, extending bandwidths, increasing gains and improving signal-to-noise ratios only when these improvements are needed [e.g. 12,15,60]. This is, of course, a form of prediction about where and when to allocate resources that depends on the physiological and behavioral state of an animal [60]. Such state dependency could be achieved by a variety of mechanisms, including neuromodulators, though more direct neural mechanisms and hormones are also likely to play a role on shorter and longer timescales, respectively.

Neuron and neural circuit structure

Detailed anatomical reconstructions, again coupled with theory and computational modelling, have shown that the morphology of the neurons, neural circuits and entire nervous systems appears to be configured to reduce energy consumption. This extends from the size and structure of single neurons [12,42,43,61] and neural tracts [62,63], to the placement of neurons within neural networks or regions within the cortex [e.g. 64-68].

The structure of single neurons

Size is a key factor in determining neuronal energy consumption and the energy efficiency of information processing. Small neurons have lower total membrane capacitance but also less membrane area in which to house ion channels and receptors, and less volume in which to accommodate mitochondria [12,42,61-63]. So, small neurons will be limited in terms of bandwidth and will be noisy but they will have low energy consumption [12,42]. Thus, whilst operating at low information rates they can be very energy efficient, far more so than their larger counterparts (see above and Box 2) [12,42].

Many invertebrate neurons have a passive soma attached through a thin neurite to the axon and dendrites, whereas in vertebrate neurons an active soma is typically interposed between them [69]. Computational modelling by Hesse and Schreiber [43] suggests that removing the soma from the main dendritic-axonal information processing axis may reduce signal attenuation from the dendrites. Thus, the structure of invertebrate neurons may be a strategy for reducing the energy costs of signaling.

Axonal tracts

Within axonal tracts, the distribution of diameters tends to be skewed towards thin axons [62,63]. Thinner axons also tend to have lower firing frequencies than thicker axons. Perge *et al.* [62] suggested that this bias towards thin axons could be explained by a law of diminishing returns (Box 2): For an axon, to double its information rate, it must more than double its firing rate. Because firing rate is linearly correlated with diameter, however, doubling the information rate more than quadruples an axon's volume with knock-on effects for its energy consumption. Under these assumptions, selection to reduce energy costs promotes information transmission at the lowest rate possible, with thicker axons encoding features that cannot be coded efficiently by thin axons [62]. However, channel noise imposes limits on the minimum diameter of axons because in very narrow axons the opening single voltage-gated Na⁺ channels becomes sufficient to trigger action potentials, reducing information rates and inflating energy consumption [63].

Wiring economy

Signal transmission along dendrites or axons (wires) has been suggested to be a substantial cost within nervous systems [5,6]. Consistent with this the placement of components within nervous systems is close to a configuration that minimizes the volume of wire at various scales from individual neurons [64-66] to brain regions [67,68]. Perhaps the clearest example of this wiring economy is in the layout of the *C. elegans* nervous system, where the positions of neurons show a striking match to the wire length minimized structure [6,64]. More recent studies have shown that, the positions of neurons within more complex neural networks in insects adhere to a wire length minimized layout when the volume of the components is considered (volume exclusion) [65]. It has also been suggested that wiring economy can explain the difference in the position of the soma in invertebrate and vertebrate neurons [66]. The placement of components within nervous systems to minimize neuronal wire produces energy savings both developmentally and operationally. Operational savings from the reduced distances over which signals must be transmitted should depend strongly on the costs of such signals, with higher spike rates and most costly action potentials being significant factors. This suggests that, although current models assume all wires have equal costs, wires should have different life time operational costs that affect component placement.

Conclusions

The processing, propagation and transmission of information in neurons and neural circuits consumes substantial amounts of energy. Determining the causes and consequences of this relationship increasingly requires studies that combine experimental approaches with theory and computational

modelling. This approach permits not only analysis of how information processing in neurons and neural circuits consumes energy but also exploration of possible relationships that could be achieved with different configurations.

Recent studies have emphasized links between basic biophysical processes in neurons, information processing and energy consumption that produce trade-offs between bandwidth, noise and energy consumption. It is these trade-offs that produce the law of diminishing returns that limits information processing in neurons and neural circuits. This law heavily penalizes information rate maximization and instead promotes a reduction to information rates that maximize the energy efficiency of information processing.

Numerous lines of evidence suggest that trade-offs between information processing and energy consumption have influenced the evolution of neurons and neural circuits at all scales from the numbers and types of molecular components they express to the composition and length of axonal tracts that link neurons. Energy efficiency in neurons and neural circuits will reduce demands on the limited energy available for the brain. However, a key principle is that resources are placed where and when they are needed. On evolutionary timescales, the information processing capacities of neurons and circuits appear to increase to that necessitated by the demands of behavior and environment but this does not necessarily mean that the energy costs must be paid throughout an animal's lifetime. Instead, resources can be differentially allocated according to state and circumstance, reducing information processing capabilities when they are least likely to be needed, thereby reducing energy costs. Given that energy limitation is likely to a strong selective pressure on the evolution of brains, energy efficiency within neurons and neural circuits is an essential part of an animal's ultimate success.

Box 1. Measuring energy consumption

Key to determining 'how' and 'why' processes consume energy is coupling the experimental measurement of neuronal energy consumption with energy budgets for particular tissues and computational modelling. This combination of approaches is crucial because direct experimental measurements of single neuron energy consumption are extremely challenging due to their size, highly-branched structure, and embeddedness within networks. Consequently, experimental measurements of oxygen consumption, carbon dioxide production or other proxies of neuronal energy consumption are typically made from larger volumes of tissue from the retina [11,13,14] to the entire brain [10,70]. With sufficient knowledge of the structure and activity of the neural tissue being measured, the energy consumed can be apportioned to various processes such as action potential transmission, synaptic transmission or transmitter recycling: a so-called 'top-down' approach.

An alternative 'bottom-up' approach is to determine the energy consumption from the biophysical and structural properties of single neurons, synapses and molecular components [e.g. 8,9]. Such an approach depends upon electrophysiological measurements of currents and conductances, as well as membrane capacitance. Recently, traditional electrophysiological methods have been augmented by live imaging of molecules that are directly involved in energy metabolism, such as ADP/ATP or NADH-NAD⁺ [71-74]. This imaging has enormous potential for estimating energy consumption within spatially extensive neurons and specific structures such as synapses [73,74], providing bounds for cellular- and subcellular-level bottom-up energy budgets. When combined with details of molecular processes that occur within neurons, such as the structure of second messenger cascades, this approach can yield detailed energy budgets for neurons that quantify the consumption of specific processes. Moreover, when coupled with dynamic computational models [26,29,41], this approach can allow the energy consumption of neurons to be estimated on a fine temporal scale equivalent to that of the electrical signals within neurons themselves.

Both approaches, top-down and bottom-up, have advantages and disadvantages in isolation but ideally bottom-up energy budgets should be corroborated with experimental measurements of energy consumption [9]. Even so, each assumption must be carefully examined.

Box 2. A law of diminishing returns

Several studies of the energy efficiency of information processing, both experimental and computational, have found that it is characterized by a law of diminishing returns [12,42,46,62]: Increasing the information processing capacity of neurons, neural circuits or components therein causes an even greater increase in energy consumption. This law arises from the basic biophysics that link information processing, in terms of bandwidth extension and increasing the signal-to-noise ratio, to neuronal energy consumption. This law has been found in through the comparative analysis of homologous neurons from different species [12], comparison of axons within tracts and nerves [62], computational modelling of compartments of different sizes [42], and manipulation of inputs into neurons using dynamic clamp [46]. For example, experimental measurements from the photoreceptors of four fly species have shown that the information rate and energy consumption increase with light intensity. Photoreceptors from large flies (e.g. blowflies) can encode approximately five times more information than those of small flies (e.g. fruit flies) [12]. However, the unit cost of information (ATP molecules hydrolyzed per bit) increases with the highest information rate achievable, producing a law of diminishing returns that penalizes overcapacity severely. Computational models also show a similar law of diminishing returns [42]: Larger compartments can achieve higher information rates than smaller compartments but do so with decreasing metabolic efficiency, so that smaller compartments can be an order of magnitude more energy efficient than larger compartments encoding the same information rate.

Conflict of interest statement

Nothing declared.

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- of special interest
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